REMARKS

Claims 19-20, 22, 23, 24, 26, 39, 46, 48, 50-57 have been canceled. Claims 1 and 31 have been amended to add a phrase "wherein the said dual retard technique is a combination of matrix formulation and reservoir formulation" to describe dual retard technique. Support for this amendment is found at page 2 in paragraph [0031].Claims 1 and 31 have also been amended to add a phrase "wherein the dosage form reduces the chances of burst effects". Support for this amendment is found at page 2, paragraph [0031]. Claims 9 and 16 have been amended to change the ratio from 100:20 to 100:30 as set forth in the specifciationat page 3, paragraphs [0041] and [0042].

Claims 1-2, 4-5, 9-13, 16-20, 22-35, 39-43 and 46-61 were rejected under 35 U.S.C. §103(a) as being unpatentable over Timmins et al. (Timmins).

Reconsideration is requested.

Many modified delivery systems utilize a matrix dosage form that provides for useful levels of controlled release in the delivery of sparingly soluble drugs. For highly soluble drugs, such matrix formulations do not provide adequate control over the release rate, instead resulting in a drug release profile that approximates first-order kinetics along with dose dumping or a burst release that makes the matrix formulatiuon unacceptable for use with soluble drugs. However, since many modified release dosage forms contain comparatively large amount of highly soluble active ingredient it is often necessary to include large amounts of suitable excipients to achieve

appropriate controlled release profiles. This results in an over sized dosage form which causes patient rejection due to the difficulty in swallowing the over sized dosage form. Hence a technique is needed, which can effectively control the release of the highly soluble active ingredient without requiring an over sized dosage form.

The Timmins patent was cited in the present specification at paragraph [0006] where the applicants distinguished Timmins from the claimed invention as follows:

> A biphasic controlled release delivery system for metformin hydrochloride, which has prolonged gastric residence and that swells following hydration. The ratio of inner solid phase to outer continuous phase is 0.5:1 to about 4:1. The major limitation of this invention (i.e. Timmins) is that it provides a very bulky formulation for higher doses of the metformin hydrochloride that is very inconvenient for human consumption. For instance, example cited provides formulation of 500mg metformin with tablet weight of 1.0gm. Hence restricting to the low dose sustained release tablets of 500mg and slightly more and making it obligatory to take two tablets of 500mg each time to provide sustain[ed] action. The cited example teaches use of combination of at least one hydrophilic polymer and which is essential part for swelling. Non-swellable or non-erodable formulations are not included in the invention.

It is clear from the brief description as well as specification that Timmins operates by increasing the time that the dosage remains in the stomach as a result of the swelling of the formulation. This essential functional characteristic can

only be achieved by the use of polymers that swell on contact with water. Therefore, although Timmins has mentioned an inner solid particulate phase and outer solid continuous phase that use one or more hydrophilic polymers, one or more hydrophobic polymer and/or one or more hydrophobic materials, the Timmins composition requires at least one hydrophilic polymer, as shown by reference to all of the enabling examples of that patent. Hence, in the implementation of the teachings of Timmins, a skilled person would be directed to use at least one hydrophilic polymer if that person was following the teachings of Timmins in making a sustained release formulation. This does not make obvious the use of the dual retard techniques, as recited in claim 1 and the other claims of the present application because that technique incorporates only hydrophobic polymers.

In the Office Action of August 31, 2010, the Examiner at page 2 urged that Timmins discloses a control release delivery system including (1) an inner solid particulate phase..., and (2) an outer solid continous phase in which the above granules of inner solid particulate phase are embedded and dispersed throughout... This that Timmins only discloses a biphasic formulation in which matrix formulation is used in both phases, inner and outer phase. The present invention uses a new technique called dual retard technique, which is a combination of matrix formulations and reservoir formulations, as pointed out in amended claim 1 and 31, instead of matrix formulation in both phases used in Timmins. In this dual retard technique, first the micromatrix particles of high solubility dose active ingredient and one or more hydrophobic release controlling agents are formed (matrix formulations) and then these are further coated (reservoir formulations) with one or more release controlling agents (micromatrix particles are not dispersed or embedded as in Timminis). This dual retard release technique

significantly reduces the amount of release controlling agents which are otherwise required in very high quantity and make the dosage form very bulky and therefore pose difficulty in swallowing. The other advantages of present invention is that it reduces the chances of dose dumping, unnecessary burst effect and failure of the system, which are otherwise usually associated with simple matrix or reservoir system.

In the present specification at paragraph [0063], it was disclosed that: "FIGS. 2 and 3 show release of high solubility active agent (5 and 6 as well as 9 and 100 as per Examples 1 and 2, respectively from a dosage form prepared using dual retard technique and release of high solubility active agent (7 and 8 as well as 11 and 12) as per Examples 3 and 4 respectively from a dosage form prepared without using dual retard release technique. The total quantity of the hydrophobic release controlling agent is same in all the dosage forms. The figures clearly show that the use of dual retard technology significantly reduces the burst effect and effectively controls the release rate of the high solubility active ingredient for a prolonged period. FIG. 4 shows release of high solubility active agent (13 and 14) as per Example 8, from a dosage form prepared using dual retard technique and release of high solubility active agent (15 and 16) as per Example 11, from a dosage form prepared without using dual retard release technique. The total quantity of the hydrophobic release controlling agent is the same in all the dosage forms. In spite of that the figures clearly show that dual retard technology significantly reduces the burst effect and effectively controls the release rate of the high solubility active ingredient for a prolonged period.

Timminis does not show any of the advantages of the cliaimed invention even though he disclosed the same problem

without giving any solution. This problem is only solved by the dual retard technique pointed out in the claims of the present application. This discovery is also confirmed by all of the examples of Timmins, wherein very high amount of polymers is used to achieve a useful controlled release profile for highly soluble drugs.

Although the Timmins patent discloses the general conditions including a large range of drug 10-98% of the inner solid particulate phase (column 9, lines 59-61), the extended release material is in the form of a hydrophobic polymer and/or other hydrophobic material in amounts within the range of about 5-95% by weight, based on the weight of the inner solid particulate phase (column 9, lines 62-67 of Timmins).

It is apparent that Timmins disclosed/claimed a very broad ranges, almost the entire range for drug and polymer, whereas claims 9, 16 and 30 point out a restricted weight ratio of drug and polymer in micromatrix particle to the very narrow range from 100:2.5 to 100:30 (about 2.4-23% of the polymer and about 76-97.5% of the active ingredient).

The weight ratio of the inner solid particulate phase to the outer solid continuous phase is within a range of 0.5:1 to 4:1 (column 9, lines 54-58 of Timmins).

The present invention has claimed up to 1500mg, which is practically possible as the final weight of the composition goes up to 2gm but considering the Timmins dose range and the amounts of polymer used in the examples, the final weight of the composition for 3000mg of drug should be around 6 gm, which is not possible to swallow.

Timmins only disclosed the amounts of polymers in terms of wide ranges and the use of hydrophobic material was never exemplified and even the complete range of polymers is not covered by the examples. A general disclosure of an entire range

does not make obvious each amount that falls within the range. The unexpected results demonstrated by the data in the drawings shows the unobious of the claimed range. In addition, the inventors have surprisingly found that the total amount of polymer is significantly reduced as compared to the prior art and gives an unexpected advantage to reduce the tablet size and prevent the burst release by using dual retard technique. Thus, It is not only optimization of the workable ranges but practical and workable ranges along with the novel and different dual retard technique.

In Timmins, the final size of the dosage form becomes very large due to large quantity of polymer required and thus the Timmins approach to formulations of drugs that must be administered in high doses, such as metformin, is not practical due the difficulty in swallowing that is very common in older patient populations. The following Table is derived from Timmins and it illustarte the high amounts of polymer relative to the active pharmaceutical ingredient (API) that result from the Timmins technique.

Example-1	500g API + 376.5g polymer	75% polymers by wt of API
Example-2	500g API + 391g polymer	78% polymers by wt of API
Example-3	500g API + 408 g polymer	81% polymers by wt of API
Example-4	500g API + >400 g polymer	81% polymers by wt of API

If we compare examples for the same drug as shown in the present specification (e.g. Example 8 = 20% polymer), the final size of

the dosage form will actually be much smaller as compared to the Timmins dosage form. Thus, it is clear from above that the problem, though mentioned in Timmins, is actually not solved by invention whereas it is actually solved in instant invention.

Although it is noted that the Timmins has covered a range of metformin from 1 to 3gms once daily, but the final tablet weight is of approximately 1gm for 500mg of drug, so one can assume a tablet weight of 6gms for 3gms of drug, which is unrealistic to consume by a patient. This is the precise reason, Timmins prior art has used 2x 500 mg dosage for its bioequivalence study (example-5) because 1000mg dosage, if prepared according to technique of Timmins, would result in unpalatable dosage form (2gm). In comparison, the tablet weight of the present invention for 500mg of dose is about 643mg, so even 1000mg dosage is formulated it would not exceed total wt of around 1300mg, which would be comparably easy to swallow. Thus, inventors of this invention has kept this thing in mind and only provided dose which have some real significance (even for 1500mg of drug, the final weight of tablet goes up to 1929mg). which is much less than the final tablet weight of Timmins.

When a reference teaches away from a claimed invention, the reference does not make the climed invention obvious. MPEP §2145 and § 2141.02. The prior art must be considered in its entirety and teachings away from the claimed invention must be considered. W.L. Gore Associates Inc. v. Garlock, Inc., 220 USPQ 303 (Fed. Cir. 1983)). In this case, Timmins teaches away from the use of hydrophobic polymers as the description states (column 2, lines 42-47) that "Hydration of any polymer matrix used to formulate the dosage form is a pre-requirement of establishing a stable release rate. Thus, a readily hydrating polymer is required to establish the desired stable release rate. However, if the polymer used is slow to

hydrate, then an undesirable variable burst can occur. It is known to a skilled person that hydration is possible only with the polymers which are hydrophilic in nature and polymers slow to hydrate are hydrophobic in nature. This statement directs one skilled in the art not to use a hydrophobic polymer if one is following Timmmins teachings.

The formulation of highly soluble drugs in a compact form results from the formulation recited in claim 1 and the other claims of the present application. An additional example of a particular drug that is amenable to formulation according to the claimed invention is sustained release levetiracetam which is approved by the Food and Drug Administration as a 500mg tablet for once daily administration. However the approved dosage and administration starts with 1000mg daily and hence two tablets (sustained release) of 500mg must be taken by the patient which is inconvenient to the patients. This appears to be a direct result of the large size that would result if prior art technology was used to formulate a 1000mg controlled release tablet. In the case of the instant invention, because of the very low quantity of polymer required, the same high dose-high solubility drug, Levetiracetam can be prepared with acceptable size even with 1000mg strength, for administration as a single dosage form. This clearly shows the advantages of the reduction in the size of conrtrolled release dosage forms according to the present invention as defined by the claims.

Timmins teaches a drug delivery system which achieves extended gastric residence by virtue of size but does degrade in vivo so as not to cause obstruction of the gastrointestinal tract. Thus, Timmins is limited to gastroretentive dosage forms and teaches away from any other type of dosage form that does not swell in the stomach in order to retard its passage in the gastrointestinal tract.

For these reasons, it is requested that this ground of rejection be withdrawn.

Claims 24, 27-28, and 29 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Timmins and Merck Index.

Reconsideration is requested.

Timmins has been distinguished from the claimed invention above as only teaching the concept of formulating a dosage form so that it swells sufficiently to be gastroretentive. The claimed dosage forms of valproic acid and niacin are not formulated to be gastroretentive and they do not have an absorption window. Thus, the teachings of Timmins can not be applied to these drugs. For these reasons, and the comments set forth above with regard to Timmins, it is respectfully submitted that claims 24, 27-28, and 29 are not obvious under 35 U.S.C.§ 103(a) over Timmins and Merck Index.

It has also been noted that Timmins discloses, in a controlled release dosage form, the formulator tries to reduce the rate of dissolution by, for example, embedding the drug in a polymer matrix or surrounding it with a polymeric barrier membrane through which drug must diffuse to be released for absorption (column 2. lines 16-33). Timmins discloses techniques either of embedding or surrounding the drug in a matrix with polymeric membrane, whereas the present invention uses a dual retard technique which is a combination of matrix and reservoir formulations. This combination is not disclosed in the prior art. The inventor of the present invention has not only simply merged both the technique, but found unexpected advantages of controlled release with reduced amount of polymer, acceptable size of tablet, to overcome the burst effect. So by the teaching of Timmins a person ordinary skilled in the art, obviously go

for any one of the technique mentioned in description but not for the combination.

For these reasons, it is requested that this ground of rejection be withdrawn.

An early and favorable action is earnestly solicited.

Respectfully submitted,

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